

## References

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## Blood dyscrasia associated with azapropazone therapy

SIR, Side effects from effective drugs are inevitable but would be less common if Data Sheet recommendations were invariably followed by prescribers. The letter from Dr Green and his colleagues<sup>1</sup> illustrates this point. Their patient, who was 80 years old, with reduced renal function was given 1200 mg azapropazone daily, twice the recommended dose. In addition, she had a history of a blood dyscrasia, given in the Data Sheet as a contraindication to the use of this drug.

Azapropazone has been in use in the United Kingdom for nine years and has provided more than two and a half million patient months treatment. To our knowledge there has been no proved case of an adverse effect involving the bone marrow during this time. We trust that Dr Green's letter will draw your readers' attention to the necessity of following Data Sheet recommendations.

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## Seatone in rheumatoid arthritis

SIR, The recent paper by Larkin *et al.*<sup>1</sup> reporting a six-month placebo controlled study of Seatone in rheumatoid arthritis invites a number of comments.

Firstly, the only statistically significant finding of this trial was the observation that six patients on Seatone felt that they had deteriorated, whereas no patients on placebo felt worse, though there was no statistical difference in the clinical parameters of the two groups. If the trial design was capable of detecting a difference between the treated and control groups, then this negative effect on the

Seatone group cannot be discounted, and the implication must surely be that Seatone is detrimental to patients with rheumatoid arthritis. If, on the other hand, this negative effect is not considered to be of significance, then by implication the trial design might not have been capable of detecting a positive difference either, and no comment either way on the efficacy of Seatone can be made. An apparently negative result may often be due to faulty trial design.<sup>2</sup>

It is interesting that none of the patients in the placebo group deteriorated over the six-month course of the study. The usual experience of rheumatoid patients on non-steroidal anti-inflammatory drugs (NSAIDs) is for about half of them to deteriorate over the course of a year.<sup>3</sup> Perhaps the placebo group was not severely affected, or perhaps there are other explanations.

The deterioration of patients on Seatone also merits further comment. In our double-blind trial<sup>4</sup> six out of 66 patients experienced an exacerbation of their symptoms, and a further two developed increased stiffness when on the active treatment. Thus an exacerbation has been observed before in the use of Seatone and may be considered to be a good sign in that the patient is very sensitive to the remedy and is responding to it, albeit with an intensification of the symptoms. Management is either to reduce the dose or to discontinue treatment until the exacerbation has settled, after which, on a lower dose a good response is usually obtained. Since Larkin *et al.* discontinued the treatment of two of their patients at the three-month stage, they might have excluded two of those who could have benefited from Seatone.

A further reason for an increase in pain and stiffness became apparent in the course of our own trial. If patients begin to feel better, they tend to increase their level of activity, using muscles which may not have been used actively for some time and undertaking heavier work than that to which they had been accustomed. Thus an apparent deterioration in parameters may mask a real improvement in the patient.

Reference is made to a recent trial from New Zealand<sup>5</sup> which purports to show from an analysis of drop-out rates that Seatone was not superior to placebo in alleviating the symptoms of rheumatoid arthritis. However, in the first six weeks of the trial when all patients were also taking naproxen, 4.3% (one out of 23) of patients on Seatone dropped out of the trial compared with 20.8% (five out of 24) of patients on placebo. At the end of a further six-week period when no patients had naproxen 70% of the Seatone patients and 83% of the placebo patients had dropped out. The numbers were insufficient to make these differences significant, and to avoid a type II statistical error in comparing the two groups at the six-week stage not less than 80 patients would be required in each treatment group. However, any suggested difference is in favour of Seatone.

The tone of the reporting of the Larkin trial could suggest a negative expectation on the part of the investigators. When they referred to our 'attempted controlled trial', they incorrectly described it as having come from the Glasgow Homoeopathic Hospital. In fact the greater part of the preliminary four-year study was carried out at the Centre for Rheumatic Diseases, and the double-blind trial

was conducted at the Glasgow Victoria Infirmary. It has been shown that expectation can have a profound effect on the outcome of even the most carefully controlled double-blind trial,<sup>6</sup> and a negative expectation can mask a genuine therapeutic effect.

Seatone is not just an inert 'health food'. It is a pharmacologically active material. A number of studies have shown its anti-inflammatory activity,<sup>7,8</sup> and a more recent publication<sup>9</sup> suggests that it is an inhibitor of prostaglandin biosynthesis. This puts Seatone pharmacologically into a category similar to that of other NSAIDs, such as aspirin, indomethacin, and naproxen, which also inhibit prostaglandin synthesis.

Preliminary results from a large double-blind study currently in progress in Paris (Billard, personal communication) seem to confirm the findings of our own trial that Seatone is of value in arthritis. We continue to monitor arthritic patients who have been on Seatone now for over eight years and who find this remedy of value, since their condition deteriorates if they discontinue it but improves again when they restart. A number of patients are maintained on a low maintenance dose, and there are a few who have been able to stop all anti-inflammatory treatment, including Seatone.

There is no good evidence to show that Seatone is ineffective in arthritis and much to show that it is of value.

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SIR, I welcome the anticipated interest of Gibson and Gibson in our paper. Their points can safely be dealt with in the order presented.

Firstly, they contend that our failure to emphasise the one significant finding—against Seatone—suggests that the trial was not powerful enough to disclose any 'positive' finding. On the contrary, our implicit suggestion is that by measuring many variables trials become 'too powerful' and bogus significant findings can occur. A fear of 'type I' statistical errors cannot logically mean that 'type II' errors are also likely.

The failure of our placebo patients to 'deteriorate properly' may reflect the recognised improvement of patients under trial conditions. Some activity parameters deteriorated, though their own assessment did not reflect this. Any suggestion that they were less severely affected is refuted by Table 1 in our paper.

We knew of the transient exacerbation described in the 1980 paper.<sup>1</sup> It occurred 'two to four weeks after starting active treatment' and 'lasted for one to two weeks, after which they made good progress'. Our two patients ceased therapy at three months and do not appear to lie in this group. The contention that improved joints may lead to increased activity and pain is interesting and would presumably nullify all trials based on pain and stiffness assessment.

The tone of our reporting reflects more our findings than our expectations, since it was written, as is customary, after the trial was performed. We correctly described the origin of the 'first attempted controlled trial' (credit where due), since the Centre for Rheumatic Diseases is not mentioned in the paper, whereas the Homoeopathic Hospital – the base of the two main authors – appears on the title page.

Expectations can affect any trial. This works either way and could explain the unique results of Gibson *et al.* – since a second-line effect is claimed for Seatone, any evidence of non-steroidal anti-inflammatory drug activity is possibly detrimental to their case.

There is thus not 'much' to show that Seatone is of value except the Gibsons' own findings and the 'preliminary results from a large double-blind study currently in progress' (a paradox?). We cannot simply discount these, but since our trials failed to confirm these findings we would be against advising patients to pay over £20 for less than one month's course of a dubious preparation. The anecdotal evidence for Seatone could be matched by that of two of our patients who were keen to buy Seatone after the trial – both were on placebo.

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